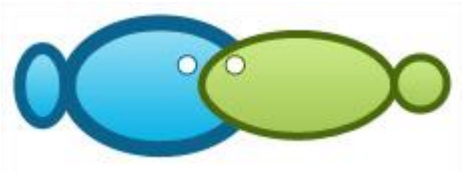

An *in-silico* study on the chemical compounds from *Macrophiothrix longipedia* as antiviral compounds against covid-19

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Abstract. *Macrophiothrix longipeda*, also known as the long-legged starfish, is an echinoderm species that exhibits important study potential, particularly within the medical field. Therefore, the present study endeavors to elucidate the chemical composition of *M. longipeda* and investigate its potential as a source of antiviral agents capable of inhibiting the Covid-19 3CLpro and RdRp enzymes derived from the human SARS-CoV-2 virus, as well as the ACE2 virus. Samples were obtained from Gili Ketapang, Indonesia, by the quadratic transect method. The samples were dried, mashed, and macerated using methanol. Identification of compound content was carried out using GC-MS, and the antiviral potential of compounds was analyzed using *in silico* molecular docking and the ADME approach. The analysis showed the presence of ten compounds, out of which 11-hydroxycephalotaxin exhibited potential synergy as an inhibitor of 3CLpro, RdRp, and hACE2. The ADME analysis offered a corroborating profile, suggesting that this compound holds promise as a viable drug candidate within the biological system. *M. longipeda* has potent antiviral activity against covid-19, by 11-hydroxycephalotaxine. Further studies are needed to prove its activity as a covid-19 antiviral agent, such as *in vitro* and *in vivo* approaches.
Key Words: 3CLpro, antiviral, covid-19, hACE2, molecular docking, RdRp.

Introduction. Echinoderms, a diverse group of marine invertebrates, are classified into five distinct classes. This taxonomic classification encompasses a wide range of species that play a vital role in both the physical and biological aspects of marine life. *Macrophiothrix longipeda*, or the long-legged starfish, is one of the marine echinoderms in the Indo-Pacific region. This animal has few studies on its morphology (Allen & Podolsky 2007), biodiversity (Hoggett 1990), phylogenetics (Podolsky & McAlister 2005), and evolutionary pathways (Hart & Podolsky 2005). Extensive studies had been conducted on the medical applications of echinoderms, with several reports emerging regarding the bioactive content. Important compounds in marine echinoderms are triterpene glycosides, which have antitumor activity (Zou et al 2003), virucidal activity (Maier et al 2001), and antiviral activity (Rodriguez et al 1991). Echinoderms also contain glycosaminoglycans (GAGs), which are mucopolysaccharides comprising amino sugar derivatives of glucosamine or galactosamine (Manivannan et al 2022). These compounds exhibit notable anticoagulant and antithrombotic properties and are commonly employed in the treatment of thrombosis. Furthermore, *in vivo* testing has been conducted, yielding promising results as an antithrombotic drug (Mulloy et al 2000). Marine echinoderms contain sphingolipids and sphingosine derivatives with neurogenic and antitumor activities (Yamada 2002; Higuchi et al 2006). Specific studies on *M. longipeda* are rare, indicating the potential for future investigation in this area. It is important to note that its

application has not been explored concerning the SARS-CoV-2 virus responsible for the covid-19 pandemic.

Echinoderms are also found in the coastal waters of Indonesia, including on Gili Ketapang Island in Probolinggo. However, there is currently no existing database record of the species found in this particular area. According to Nugroho et al (2023), the identified samples from Gili Ketapang Island included species such as *Diadema setosum, M. longipeda, Archaster typicus, Echinometra mathaei, Holothuria atra, Linckia laevigata, Bohadschia argus*, and *Ophiactis savignyi* and the dominant species was *M. longipeda*.

SARS-CoV-2 is an RNA virus known for its ability to infect the human respiratory system and possesses remarkable transmission capabilities (Zhou et al 2020). The pathogenesis of this virus begins with the attachment of its spike protein to the human ACE2 (Angiotensin Converting Enzyme 2) receptor (Walls et al 2020). This attachment is facilitated by the transmembrane protein serine 2 (TMPRSS2) (Hoffmann et al 2020), leading to activation. Subsequently, the replication cycle is initiated, involving two crucial enzymes: 3CLpro (3C-like protease) (Ahmad et al 2021) and RdRp (RNA-dependent RNA polymerase) (Shannon et al 2020). Therefore, a way to block the infection and its replication is through the inhibition of 3CLpro, RdRp, and ACE2. This study aims to identify the content of bioactive compounds in starfish extract, specifically its essential oils through GCMS, and the potential as an antiviral agent against SARS-CoV-2 by inhibiting 3CLpro, RdRp, and ACE2, through an *in-silico* approach. This study may bring new information about this species in Indonesia.

Material and Method

Sample collection. Purposive sampling with the quadratic transects method was used to collect samples from 2 stations in Gili Ketapang, located in the district of Sumberasih in Probolinggo Regency of East Java (Figure 1). After being collected, the samples were transported to the Zoology Laboratory, Nahdlatul Ulama Pasuruan Institute of Technology & Science, East Java, where they were kept in ice boxes. Echinoderms were sampled using the square transect method twice along the transect of each location. A 1x1 m paralon frame was utilized for the sampling plot, and the transect was drawn 100 m perpendicular to the coastline. Observations were made at low tide, with observation plot sites placed every 10, 30, and 50 m along the transect line, separating the transects.

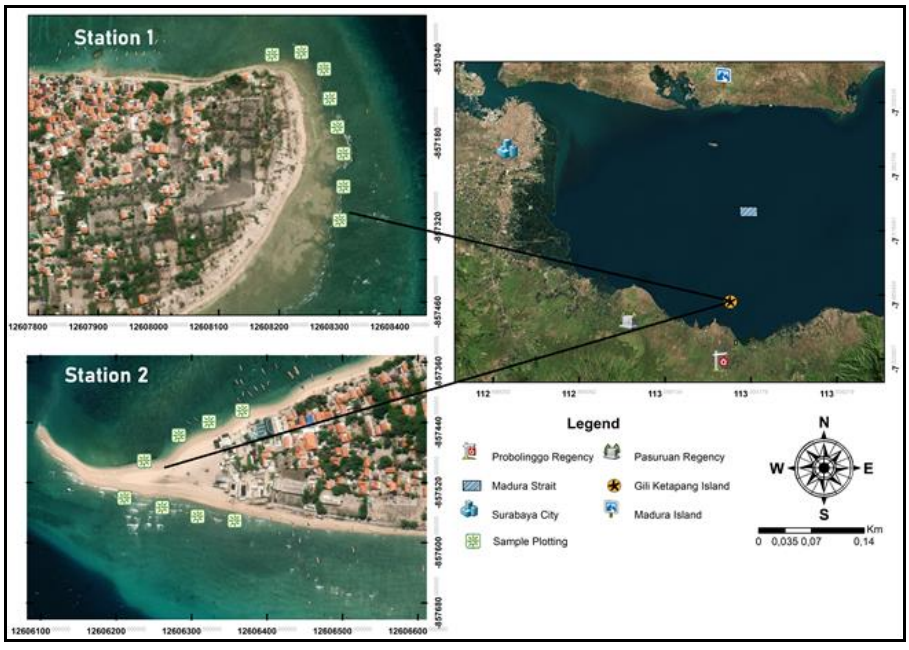

Figure 1. The location of Gili Ketapang, located in the district of Sumberasih in Probolinggo Regency of East Java.

Preparation and extraction from samples. Samples of *M. longipeda* were dried and mashed, then macerated using methanol p.a with a ratio of 1:4 (w/v) for 1x24 h. Subsequently, the mixture was separated with filter paper using a Buchner funnel and a vacuum pump, and an extract was obtained. The extract obtained was concentrated using a rotary vacuum evaporator to obtain a concentrated extract.

GCMS analysis. The concentrated extract of *M. longipeda* was analyzed using GCMS to obtain data on the content of bioactive compounds. Agilent 8890 GC and 19091S-433UI columns (30 m × 250 m x 0.25 m) were used for the analysis. The sample (100 mL) was heated for 18 minutes at a temperature rise of 100°C per minute between 60 and 325°C, and 1 mL min^{-1} of helium gas was used as the transport medium. To achieve the desired conditions, the sample was injected, and a separation ratio of 1:10 was employed. The injector was heated to 280°C, and the interaction of the Mass Spectrometer (MS) occurred at 280°C for the ion source and 150°C for the second ion source. The bioactive compound was measured at 70 eV and in the 200-700 amu reading range with NIST and Willey Library.

Molecular docking analysis. Molecular docking is a valuable technique employed to predict the potential of a compound as a drug candidate (Manivannan et al 2022). The ligand structure is depicted in Figure 2.

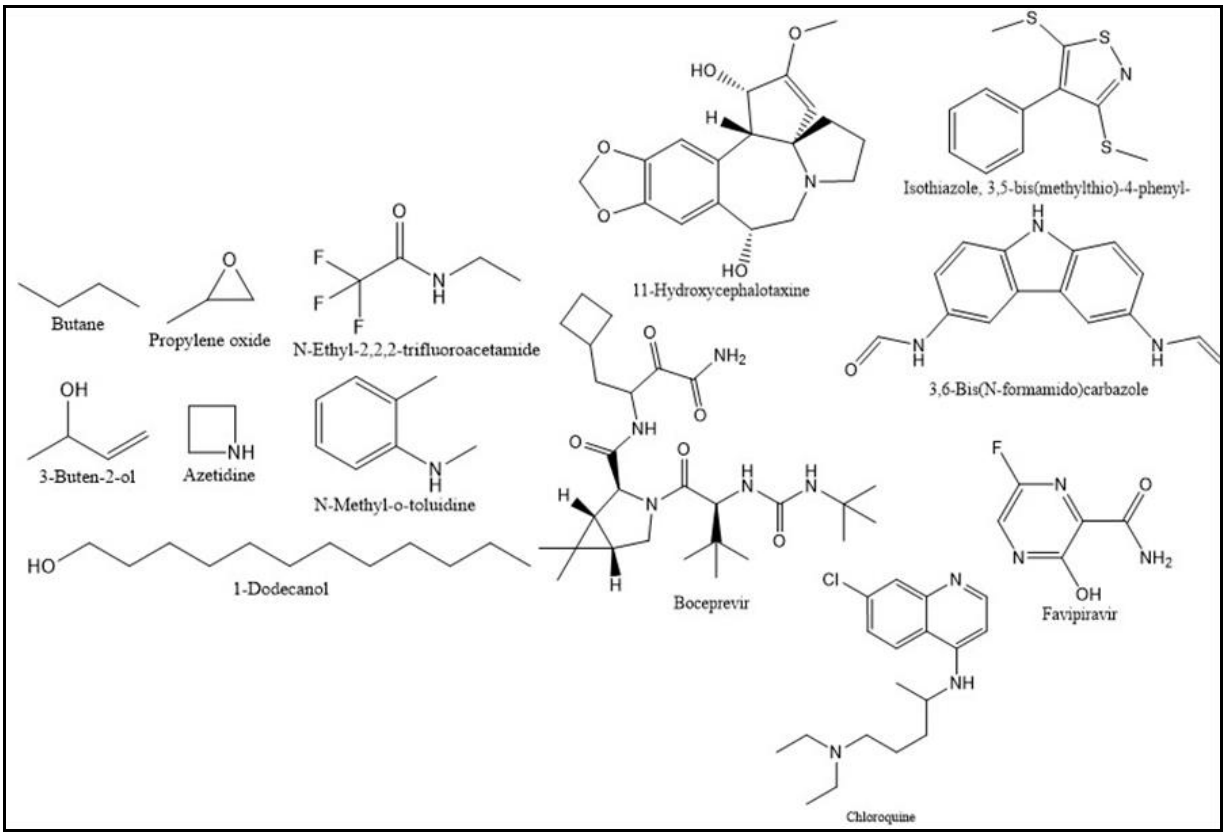

Figure 2. Structure of the ligand.

In this study, the $3CL^{pro}$ receptor was used with the control drug boceprevir (Njoroge et al 2008), and RdRp and ACE2 act as favipiravir (Cai et al 2020) and chloroquine control (Wang et al 2020). The drug compound favipiravir is a medicinal compound used to overcome influenza outbreaks by inhibiting RdRp of influenza A and B viruses (Jin et al 2013), providing good effectiveness in handling Covid-19 in Japan and China (Hogan et al 2020). Chloroquine is a medication commonly used for the treatment of malaria. Its mechanism of action involves inhibiting the heme polymerase enzyme in malaria trophozoites, which prevents the conversion of heme to hemozoin (Herraiz et al 2019).

Additionally, chloroquine has been found to inhibit the ACE2 terminal glycosylation (Vincent et al 2005). Boceprevir is a protease inhibitor used to treat hepatitis caused by hepatitis C virus (HCV) genotype 1 (Degertekin & Lok 2008). The three drugs are FDA-approved drugs used in the treatment of covid-19.

Protein preparation. Protein 3D conformers of ACE2 (PDB ID: 7VX5), RdRp (PDB ID: 7DFG), and 3CLpro (PDB ID: 7WYP) were obtained from the RCSB webserver (rcsb.org). The active site of each receptor was identified using Discovery Studio and then sterilized to remove unnecessary molecules. Furthermore, the conformers obtained were inputted as macromolecules in the PyRx software.

Ligand preparation. The identified bioactive compounds from the GCMS analysis were downloaded the 3D structure from the Pubchem server (pubchem.ncbi.nlm.nih.gov) and minimized with OpenBabel in the PyRx program. The minimization obtained a structure flexible and ready for docking (Sururi et al 2022).
Docking. Molecular docking simulations were conducted using the Vina Wizard program (Trott & Olson 2010) on the PyRx software through the protein and at the following positions: ACE2 (X: 161.262000; Y: 204.724875; Z: 284.353208), RdRp (X: 128.933609; Y: 131.912522; Z: 140.694652), and 3CLpro (X: 15.349000; Y: -13.021278; Z: 1.423000). Meanwhile, the comparators were chloroquine, favipiravir, and boceprevir. The simulation determined the value of the binding affinity of each compound and compared the results with the control compound.

Interaction and visualization. The obtained docking conformers interacted with PyMOL and were visualized with the Discovery Studio to obtain positional data and the type of interaction between the receptor-ligand. The analysis was conducted by comparing the bonds and positions similar to the control compound.

Pharmacokinetic absorption, distribution, metabolism and excretion (ADME). ADME analysis was performed using the SwissADME webserver (swissadme.ch) (Daina et al 2017) with Lipinski's drug likeness rule, bioavailability, gastrointestinal (GI) absorption, brain barrier protein (BBB) permeability, P-glycoprotein (P-gp) substrate, cytochrome (CYP) inhibitor, and skin permeation. ADME analysis determined the profile of the compound as a drug compound in the body. The parameters from Lipinski's rule of five for predicting the potential of a compound as a drug are: molar mass (≤500 kDa), hydrogen bond donors (≤5), hydrogen bond acceptors (≤10), lipophilicity (log P) (≤5), and molar refraction (40-130) (Lipinski 2004). Compounds that meet at least three parameters of Lipinski's rule have the potential to be considered drug candidates.

GI absorption refers to the capacity of a drug to be assimilated within the body. An optimal level of drug absorption corresponds to a high degree of GI absorption. Consequently, compounds exhibiting elevated values can be considered efficacious drugs due to their favorable absorption characteristics (Hoff et al 2003). In addition, this compound has no potential to pass through the brain barrier protein (BBB). The BBB is a physiological barrier consisting of a layer of microvascular endothelial cells of the brain separating the layer from the bloodstream (Lin et al 2003). The parameter is the substrate for P-gp, a crucial pump that significantly influences the absorption and elimination of drug compounds. In general, drugs exhibiting favorable therapeutic qualities are typically not classified as P-gp substrates. A P-gp substrate compound is actively pumped out, which can limit the absorption and reduce efficacy (Elmeliegy et al 2020).

Results and Discussion

M. longipeda bioactive compounds identification. The methanol used has a high polarity to produce an improved yield (Rydberg 2004) for the identification of the identified compounds. Figure 3 and Table 1 show that there were 10 bioactive

compounds determined. GCMS identified the content of volatile compounds, specifically the oils, and the structures of the identified compounds are presented in Figure 3.

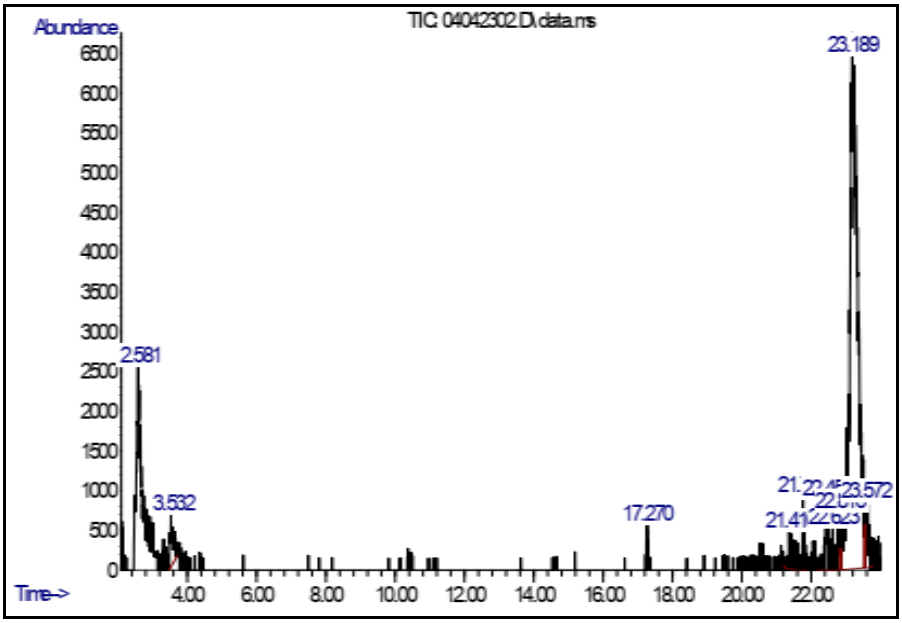

Figure 3. GCMS chromatogram of *Macrophiothrix longipeda* extract.

Table 1

Compound content in *Macrophiothrix longipeda* extract and binding affinity with control compounds

Peak	*RT (min)*	*Composition (%)*	*Compound*	*Binding affinity (kcal mol^{-1})*		
				3CL^{pro}	*RdRp*	*ACE2*
1	2.581	15.96	Butane	-2.5	-2.7	-2.7
2	3.52	2.53	Propylene oxide	-2.6	-2.7	-2.4
3	17.27	1.07	N-ethyl-2,2,2-trifluoroacetamide	-4.1	-4.1	-4.3
4	21.41	1.36	3-buten-2-ol	-3	-3.1	-3.3
5	21.76	0.99	1-dodecanol	-3.8	-3.5	-4.5
6	22.456	3.46	Azetidine	-2.9	-2.8	-2.7
7	22.623	0.49	N-methyl-o-toluidine	-4.4	-4.3	-4.6
8	22.816	1.78	11-hydroxycephalotaxine	-6.7	-6.9	-7.2
9	23.189	69.66	Isothiazole, 3,5-bis(methylthio)-4-phenyl-	-4.2	-4.8	-4.9
10	23.572	2.7	3,6-bis(N-formamido) carbazole	-6.1	-6	-7
-	-	-	Boceprevir (control drug)	-6.7	-	-
-	-	-	Favipiravir (control drug)	-	-5.1	-
-	-	-	Chloroquine (control drug)	-	-	-5.8

Note: RT - retention time.

Molecular docking analysis. The results of molecular docking analysis presented in Table 1 showed that ten compounds in *M. longipeda* form complexes with negative binding affinity values. This study showed that one compound had a lower binding affinity value than the control drug synergistically with the third receptor, namely 11-hydroxycephalotaxine, with a value of -6.7, -6,9, and -7.2 kcal mol^{-1}, for 3CL^{pro},RdRp, and ACE2, respectively.

The visualization results in Figures 4 (for 3CL^{pro}), 5 (RdRp), and 6 (ACE2) showed that the compounds form complexes with each receptor with hydrogen and hydrophobic bonds (Kharisma et al 2021). Hydrogen bonds are formed by the interaction of H atoms with F, O, and N (Głowacki et al 2013). A stable complex has no unfavorable bonds (Yamada et al 2022), and the results show that the compounds with each receptor support the potentiates as 3CL^{pro} and RdRp inhibitors of the SARS-CoV-2 virus and human ACE2. In addition, the compounds have similar inhibition positions with the

control in each receptor. This similarity illustrates that the compounds have similar inhibitory abilities to the drugs (Freire 2008).

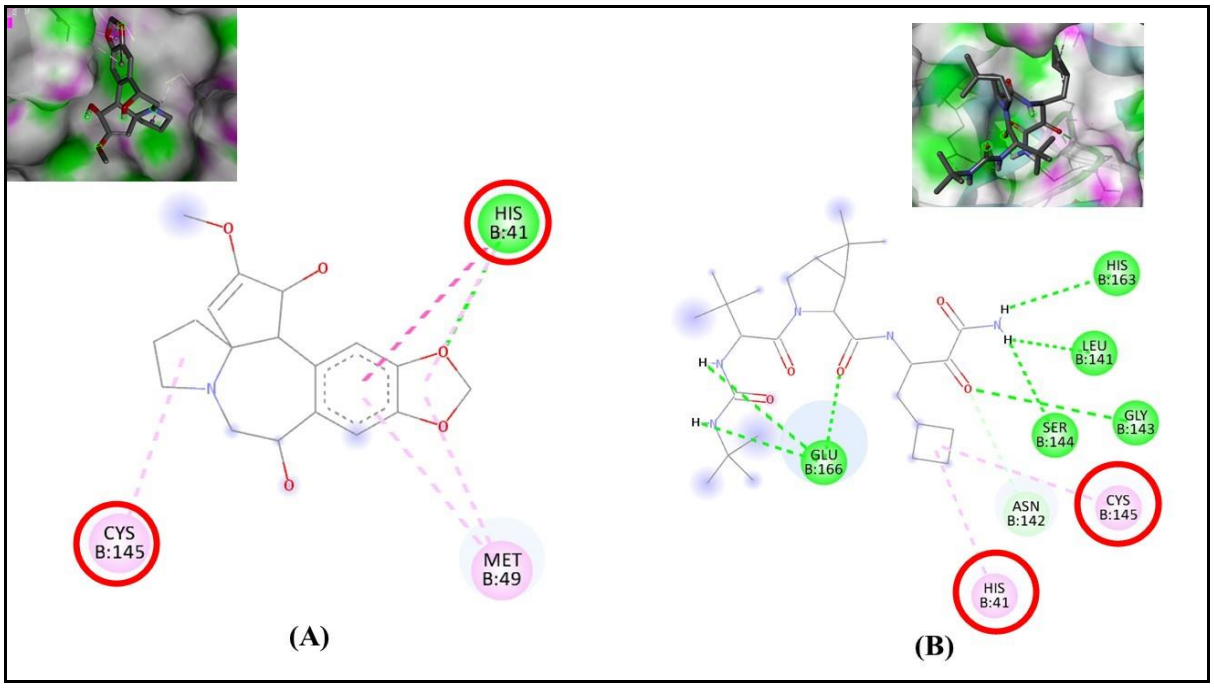

Figure 4. Visualization of compound interactions (A) and control drugs (B) with $3CL^{pro}$.

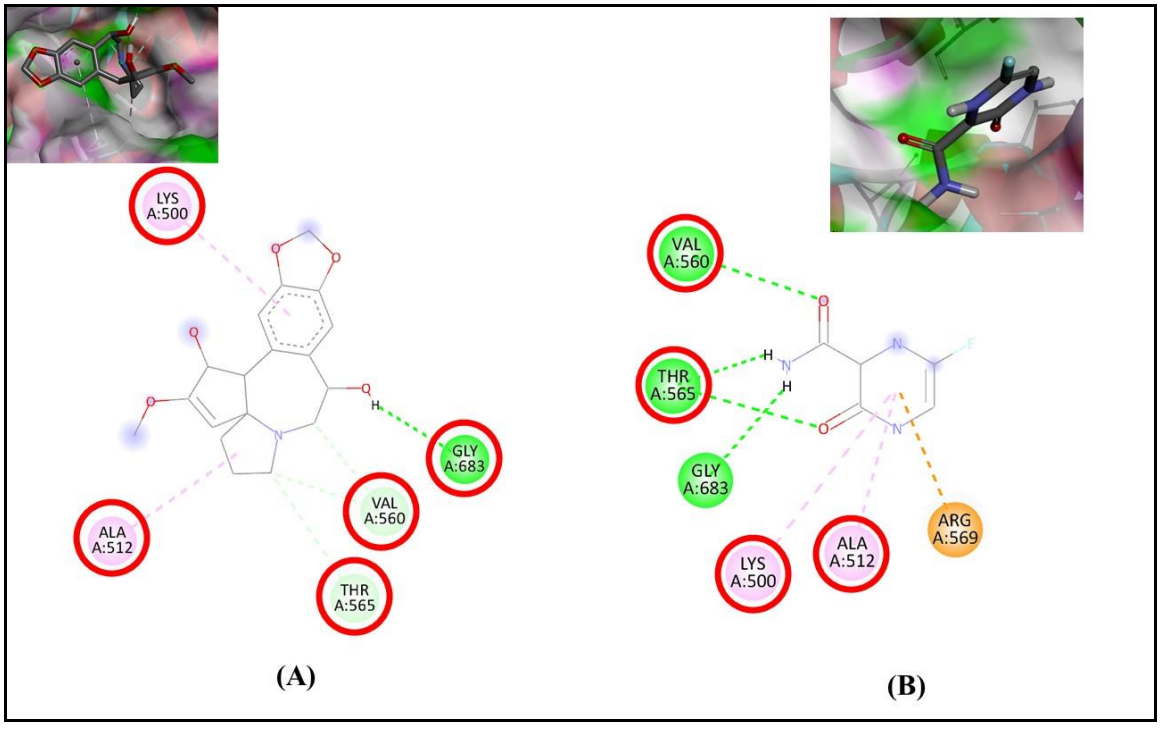

Figure 5. Visualization of compound interactions (A) and control drugs (B) with RdRp

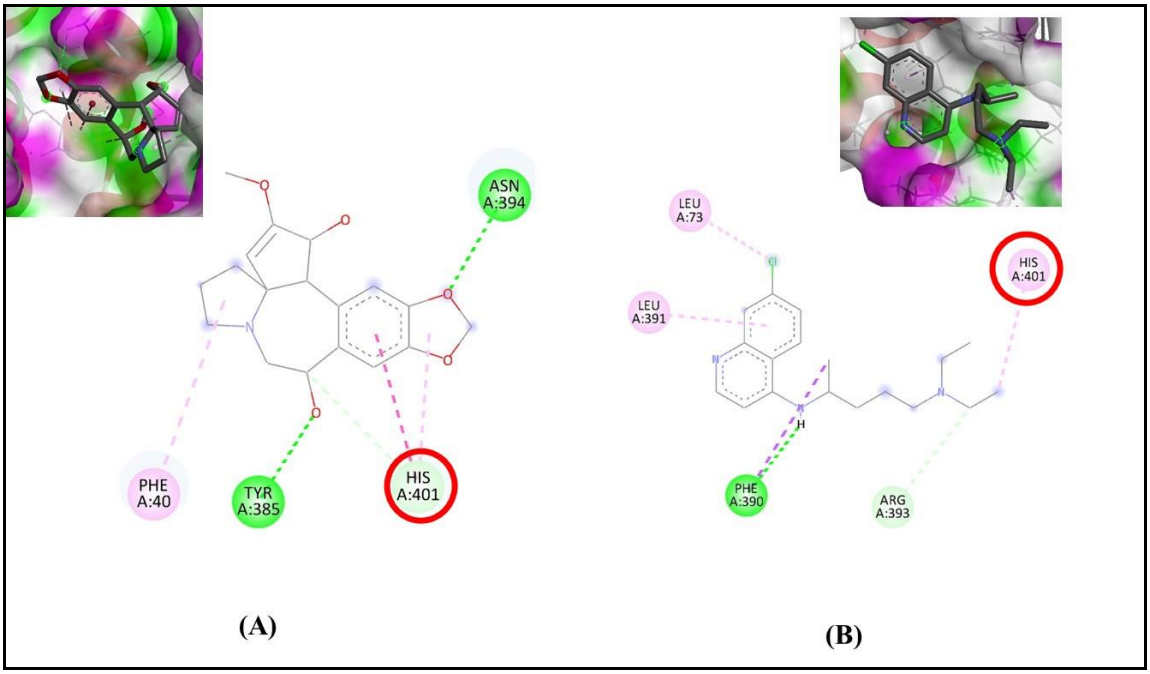

Figure 6. Visualization of compound interactions (A) and control drugs (B) with ACE2.

ADME analysis. In this study, the compound demonstrated adherence to all five Lipinski rules (Ro5) and exhibited a favorable bioavailability value of 0.55 (Table 2). Therefore, the compound has the potential to be an effective oral drug readily absorbed by the body. Bioavailability is closely related to permeability, and a good score (ABS) indicates that the drug is suitable for oral administration and efficiently absorbed into the body (Martin 2005).

Table 2

Pharmacokinetic ADME analysis

Parameter	*Score*
Molar mass	331.36
Hydrogen bond donor	6
Hydrogen bond acceptor	2
Log P (lipophilicity)	0.36
Molar refractivity	89.14
Drug likeness Lipinski	Yes
Bioavailability score	0.55
GI absorption	High
BBB permeability	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A inhibitor	No
Log K_p (cm s^{-1})	-8.07

The metabolic parameters, especially the cytochrome P450 (CYP) enzymes and the isoform family, play an essential role in drug metabolism. Furthermore, a good drug does not have inhibition of activity against this enzyme. The compounds have inhibition of activity against CYP2D6, with this enzyme having a role in xenobiotic metabolism, especially in the liver and brain (Wang et al 2009). Therefore, drug compounds targeting

receptors in the liver and brain can be removed when these compounds have inhibitory activity against CYP2D6 enzymes (Wang et al 2014). The compound 11-hydroxycephalotaxin has the potential to target ACE2 as one of the entry points for the SARS-CoV-2 virus, with a small fraction of expression in the liver (Cuervo & Grandvaux 2020).

Conclusions. 10 compunds were identified in the methanol extract of *M. longipeda*. A particular compound, namely 11-hydroxycephalotaxine, exhibits promising potential as an antiviral against covid-19. Its ADME profile substantiates its viability as a suitable candidate for an oral drug. However, additional study is imperative to establish its effectiveness in both *in vitro* and *in vivo* settings.

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Conflict of Interest. The authors declare that there is no conflict of interest.

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